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L10	L9 and asthma	91	L10
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L2: Entry 5 of 5 File: USPT Jan 12, 1999

US-PAT-NO: 5858974
DOCUMENT-IDENTIFIER: US 5858974 A

TITLE: Anti-fungal peptides

DATE-ISSUED: January 12, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Little, II; Roger G.	Benicia	CA		
Lim; Edward	Walnut Creek	CA		
Fadem; Mitchell B.	Carmel Valley	CA		

US-CL-CURRENT: 514/12; 514/11, 514/13, 514/14, 514/15, 514/16, 514/17, 514/9, 530/317, 530/324, 530/327, 530/328, 530/329

CLAIMS:

What is claimed is:

1. A peptide which has an amino acid sequence of human bactericidal/permeability-increasing protein (BPI) from about position 148 to about position 161 of SEQ ID NO: 251 and variants of the sequence having antifungal activity.

2. A peptide according to claim 1 selected from the group consisting of the peptides of SEQ. ID NOS: 205-250 as listed in Table 1.

3. A peptide according to claim 1 having from six to fourteen amino acids.

4. An antifungal peptide having from six to fourteen amino acids comprising:

(a) a core sequence of amino acids selected from the group consisting of LIQL, IQLF, WLIQL, LIQLF, and WLIQLF; and

(b) one or more cationic amino acids selected from the group consisting of K, R, H, ornithine and diaminobutyric acid at the amino and/or carboxy terminal portion of the core sequence.

5. A peptide according to claim 4 wherein the core sequence amino acids comprise amino acids in reverse sequence order.

6. A peptide according to claim 1, 3 or 4 having one or more D-isomer amino acids.

7. A peptide according to claim 1, 3 or 4 wherein the amino terminal residue is acetylated.

8. A cyclic peptide according to claim 1, 3 or 4.

9. A pharmaceutical composition comprising a peptide according to claim 1, 2, 3

or 4 and a pharmaceutically acceptable diluent, adjuvant or carrier.

10. An in vitro method for killing or inhibiting replication of fungi comprising contacting the fungi with a peptide according to claim 1, 2, 3 or 4.

11. A method of treating fungal infections comprising administering to a subject suffering from a fungal infection a therapeutically effective amount of a peptide according to claim 1, 2, 3 or 4.

12. A method according to claim 11 wherein the fungal infection involves a fungal species selected from the group consisting of Candida, Aspergillus and Cryptococcus species.

13. A method according to claim 12 wherein the Candida species is selected from the group consisting of C. albicans, C. glabrata, C. krusei, C. lusitaniae, C. parapsilosis and C. tropicalis.

14. A method according to claim 12 wherein the peptide is administered topically, intravenously, orally or as an aerosol.

15. A method according to claim 11 comprising the additional step of administering a non-peptide anti-fungal agent.

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L2: Entry 5 of 5 File: USPT Jan 12, 1999

US-PAT-NO: 5858974
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TITLE: Anti-fungal peptides

DATE-ISSUED: January 12, 1999

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Little, II; Roger G.	Benicia	CA		
Lim; Edward	Walnut Creek	CA		
Fadem; Mitchell B.	Carmel Valley	CA		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
XOMA Corporation	Berkeley	CA			02

APPL-NO: 08/ 621259 [PALM]
DATE FILED: March 21, 1996

PARENT-CASE:
This is a continuation-in-part of U.S. patent application Ser. No. 08/504,841 filed Jul. 20, 1995 now pending, herein incorporated by reference.

INT-CL: [06] A61 K 38/00, A61 K 38/02, C07 K 5/00, C07 K 7/00

US-CL-ISSUED: 514/12; 514/9, 514/11, 514/13, 514/14, 514/15, 514/16, 514/17, 530/317, 530/324, 530/327, 530/328, 530/329
US-CL-CURRENT: 514/12; 514/11, 514/13, 514/14, 514/15, 514/16, 514/17, 514/9, 530/317, 530/324, 530/327, 530/328, 530/329

FIELD-OF-SEARCH: 530/324, 530/325, 530/327, 530/326, 530/328, 530/329, 530/317, 514/12, 514/13, 514/14, 514/15, 514/16, 514/17, 514/9, 514/11

PRIOR-ART-DISCLOSED:

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Search Selected | Search ALL

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ART-UNIT: 164

PRIMARY-EXAMINER: Davenport; Avis M.

ATTY-AGENT-FIRM: McAndrews, Held & Malloy, Ltd.

ABSTRACT:

The present invention relates generally to anti-fungal peptides derived from or based on Domain III (amino aids 142-169) of bactericidal/permeability-increasing protein (BPI) and in vivo or in vitro uses of such peptides.

15 Claims, 10 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 10

BRIEF SUMMARY:

1 BACKGROUND OF THE INVENTION

2 The present invention relates generally to anti-fungal peptides derived from or

based on Domain III (amino acids 142-169) of bactericidal/permeability-increasing protein (BPI) and therapeutic uses of such peptides.

3 BPI is a protein isolated from the granules of mammalian polymorphonuclear leukocytes (PMNs or neutrophils), which are blood cells essential in the defense against invading microorganisms. Human BPI protein has been isolated from PMNs by acid extraction combined with either ion exchange chromatography [Elsbach, J. Biol. Chem., 254:11000 (1979)] or E. coli affinity chromatography [Weiss, et al., Blood, 69:652 (1987)]. BPI obtained in such a manner is referred to herein as natural BPI and has been shown to have potent bactericidal activity against a broad spectrum of gram-negative bacteria. The molecular weight of human BPI is approximately 55,000 daltons (55 kD). The amino acid sequence of the entire human BPI protein and the nucleic acid sequence of DNA encoding the protein have been reported in FIG. 1 of Gray et al., J. Biol. Chem., 264:9505 (1989), incorporated herein by reference. The Gray et al. DNA and amino acid sequences are set out in SEQ ID NOS: 251 and 252 hereto.

4 BPI is a strongly cationic protein. The N-terminal half of BPI accounts for the high net positive charge; the C-terminal half of the molecule has a net charge of -3. [Elsbach and Weiss (1981), supra.] A proteolytic N-terminal fragment of BPI having a molecular weight of about 25 kD has an amphipathic character, containing alternating hydrophobic and hydrophilic regions. This N-terminal fragment of human BPI possesses the anti-bacterial efficacy of the naturally-derived 55 kD human BPI holoprotein. [Ooi et al., J. Bio. Chem., 262:14891-14894 (1987)]. In contrast to the N-terminal portion, the C-terminal region of the isolated human BPI protein displays only slightly detectable anti-bacterial activity against gram-negative organisms. [Ooi et al., J. Exp. Med., 174:649 (1991).] An N-terminal BPI fragment of approximately 23 kD, referred to as "rBPI.sub.23," has been produced by recombinant means and also retains anti-bacterial activity against gram-negative organisms [Gazzano-Santoro et al., Infect. Immun. 60:4754-4761 (1992)]. In that publication, an expression vector was used as a source of DNA encoding a recombinant expression product (rBPI.sub.23). The vector was constructed to encode the 31-residue signal sequence and the first 199 amino acids of the N-terminus of the mature human BPI, as set out in SEQ ID NOS: 251 and 252 taken from Gray et al., supra, except that valine at position 151 is specified by GTG rather than GTC and residue 185 is glutamic acid (specified by GAG) rather than lysine (specified by AAG). Recombinant holoprotein, also referred to as rBPI, has also been produced having the sequence set out in SEQ ID NOS: 251 and 252 taken from Gray et al., supra, with the exceptions noted for rBPI.sub.23. An N-terminal fragment analog designated rBPI.sub.21 or rBPI.sub.21 .DELTA.cys has been described in co-owned, copending U.S. Pat. No. 5,420,019 which is incorporated herein by reference. This analog comprises the first 193 amino acids of BPI holoprotein as set out in SEQ ID NOS: 251 and 252 but wherein the cysteine at residue number 132 is substituted with alanine, and with the exceptions noted for rBPI.sub.23.

5 The bactericidal effect of BPI has been reported to be highly specific to gram-negative species, e.g., in Elsbach and Weiss, Inflammation: Basic Principles and Clinical Correlates, eds. Gallin et al., Chapter 30, Raven Press, Ltd. (1992). BPI is commonly thought to be non-toxic for other microorganisms, including yeast, and for higher eukaryotic cells. Elsbach and Weiss (1992), supra, reported that BPI exhibits anti-bacterial activity towards a broad range of gram-negative bacteria at concentrations as low as 10.sup.-8 to 10.sup.-9 M, but that 100- to 1,000-fold higher concentrations of BPI were non-toxic to all of the gram-positive bacterial species, yeasts, and higher eukaryotic cells tested at that time. It was also reported that BPI at a concentration of 10.sup.-6 M or 160 .mu.g/ml had no toxic effect, when tested at a pH of either 7.0 or 5.5, on the gram-positive organisms Staphylococcus aureus (four strains), Staphylococcus epidermidis, Streptococcus faecalis, Bacillus subtilis, Micrococcus lysodeikticus, and Listeria monocytogenes. BPI at 10.sup.-6 M reportedly had no toxic effect on the fungi Candida albicans and Candida parapsilosis at pH 7.0 or 5.5, and was non-toxic to higher eukaryotic

cells such as human, rabbit and sheep red blood cells and several human tumor cell lines. See also Elsbach and Weiss, Advances in Inflammation Research, ed. G. Weissmann, Vol. 2, pages 95-113 Raven Press (1981). This reported target cell specificity was believed to be the result of the strong attraction of BPI for lipopolysaccharide (LPS), which is unique to the outer membrane (or envelope) of gram-negative organisms.

6 The precise mechanism by which BPI kills gram-negative bacteria is not yet completely elucidated, but it is believed that BPI must first bind to the surface of the bacteria through hydrophobic and electrostatic interactions between the cationic BPI protein and negatively charged sites on LPS. LPS has been referred to as "endotoxin" because of the potent inflammatory response that it stimulates, i.e., the release of mediators by host inflammatory cells which may ultimately result in irreversible endotoxic shock. BPI binds to lipid A, reported to be the most toxic and most biologically active component of LPS.

7 In susceptible gram-negative bacteria, BPI binding is thought to disrupt LPS structure, leading to activation of bacterial enzymes that degrade phospholipids and peptidoglycans, altering the permeability of the cell's outer membrane, and initiating events that ultimately lead to cell death. [Elsbach and Weiss (1992), supra]. BPI is thought to act in two stages. The first is a sublethal stage that is characterized by immediate growth arrest, permeabilization of the outer membrane and selective activation of bacterial enzymes that hydrolyze phospholipids and peptidoglycans. Bacteria at this stage can be rescued by growth in serum albumin supplemented media [Mannion et al., J. Clin. Invest., 85:853-860 (1990)]. The second stage, defined by growth inhibition that cannot be reversed by serum albumin, occurs after prolonged exposure of the bacteria to BPI and is characterized by extensive physiologic and structural changes, including apparent damage to the inner cytoplasmic membrane.

8 Initial binding of BPI to LPS leads to organizational changes that probably result from binding to the anionic groups in the KDO region of LPS, which normally stabilize the outer membrane through binding of Mg.sup.++ and Ca.sup.++. Attachment of BPI to the outer membrane of gram-negative bacteria produces rapid permeabilization of the outer membrane to hydrophobic agents such as actinomycin D. Binding of BPI and subsequent gram-negative bacterial killing depends, at least in part, upon the LPS polysaccharide chain length, with long O-chain bearing, "smooth" organisms being more resistant to BPI bactericidal effects than short O-chain bearing, "rough" organisms [Weiss et al., J. Clin. Invest. 65: 619-628 (1980)]. This first stage of BPI action, permeabilization of the gram-negative outer envelope, is reversible upon dissociation of the BPI, a process requiring the presence of divalent cations and synthesis of new LPS [Weiss et al., J. Immunol. 132:3109-3115 (1984)]. Loss of gram-negative bacterial viability, however, is not reversed by processes which restore the envelope integrity, suggesting that the bactericidal action is mediated by additional lesions induced in the target organism and which may be situated at the cytoplasmic membrane [Mannion et al., J. Clin. Invest. 86:631-641 (1990)]. Specific investigation of this possibility has shown that on a molar basis BPI is at least as inhibitory of cytoplasmic membrane vesicle function as polymyxin B [In't Veld et al., Infection and Immunity 56:1203-1208 (1988)] but the exact mechanism as well as the relevance of such vesicles to studies of intact organisms has not yet been elucidated.

9 Three separate functional domains within the recombinant 23 kD N-terminal BPI sequence have been discovered [Little et al., J. Biol. Chem. 269:1865 (1994)]. These functional domains of BPI designate a region of the amino acid sequence of BPI that contributes to the total biological activity of the protein and were essentially defmed by the activities of proteolytic cleavage fragments, overlapping 15-mer peptides and other synthetic peptides. Domain I is defined as the amino acid sequence of BPI comprising from about amino acid 17 to about amino acid 45. Peptides based on this domain are moderately active in both the inhibition of LPS-induced LAL activity and in heparin binding assays, and do not exhibit significant bactericidal activity. Domain II is defined as the amino acid sequence of BPI comprising from about amino acid 65 to about amino

acid 99. Peptides based on this domain exhibit high LPS and heparin binding capacity and are bactericidal. Domain m is defined as the amino acid sequence of BPI comprising from about amino acid 142 to about amino acid 169. Peptides based on this domain exhibit high LPS and heparin binding activity and are bactericidal. The biological activities of functional domain peptides may include LPS binding, LPS neutralization, heparin binding, heparin neutralization or bactericidal activity.

10 Fungi are eukaryotic cells that may reproduce sexually or asexually and may be biphasic, with one form in nature and a different form in the infected host. Fungal diseases are referred to as mycoses. Some mycoses are endemic, i.e. infection is acquired in the geographic area that is the natural habitat of that fungus. These endemic mycoses are usually self-limited and minimally symptomatic. Some mycoses are chiefly opportunistic, occurring in immunocompromised patients such as organ transplant patients, cancer patients undergoing chemotherapy, burn patients, AIDS patients, or patients with diabetic ketoacidosis.

11 Fungal infections are becoming a major health concern for a number of reasons, including the limited number of anti-fungal agents available, the increasing incidence of species resistant to older anti-fungal agents, and the growing population of immunocompromised patients at risk for opportunistic fungal infections. The incidence of systemic fungal infections increased 600% in teaching hospitals and 220% in non-teaching hospitals during the 1980's. The most common clinical isolate is Candida albicans (comprising about 19% of all isolates). In one study, nearly 40% of all deaths from hospital-acquired infections were due to fungi. [Sternberg, Science, 266:1632-1634 (1994).]

12 Anti-fungal agents include three main groups. The major group includes polyene derivatives, including amphotericin B and the structurally related compounds nystatin and pimaricin. These are broad-spectrum anti-fungals that bind to ergosterol, a component of fungal cell membranes, and thereby disrupt the membranes. Amphotericin B is usually effective for systemic mycoses, but its administration is limited by toxic effects that include fever and kidney damage, and other accompanying side effects such as anemia, low blood pressure, headache, nausea, vomiting and phlebitis. The unrelated anti-fungal agent flucytosine (5-fluorocytosine), an orally absorbed drug, is frequently used as an adjunct to amphotericin B treatment for some forms of candidiasis and cryptococcal meningitis. Its adverse effects include bone marrow depression with leukopenia and thrombocytopenia.

13 The second major group of anti-fungal agents includes azole derivatives which impair synthesis of ergosterol and lead to accumulation of metabolites that disrupt the function of fungal membrane-bound enzyme systems (e.g., cytochrome P450) and inhibit fungal growth. Significant inhibition of mammalian P450 results in significant drug interactions. This group of agents includes ketoconazole, clotrimazole, miconazole, econazole, butoconazole, oxiconazole, sulconazole, terconazole, fluconazole and itraconazole. These agents may be administered to treat systemic mycoses. Ketoconazole, an orally administered imidazole, is used to treat nonmeningeal blastomycosis, histoplasmosis, coccidioidomycosis and paracoccidioidomycosis in non-immunocompromised patients, and is also useful for oral and esophageal candidiasis. Adverse effects include rare drug-induced hepatitis; ketoconazole is also contraindicated in pregnancy. Itraconazole appears to have fewer side effects than ketoconazole and is used for most of the same indications. Fluconazole also has fewer side effects than ketoconazole and is used for oral and esophageal candidiasis and cryptococcal meningitis. Miconazole is a parenteral imidazole with efficacy in coccidioidomycosis and several other mycoses, but has side effects including hyperlipidemia and hyponatremia.

14 The third major group of anti-fungal agents includes allylamines-thiocarbamates, which are generally used to treat skin infections. This group includes tolnaftate and naftifine.

15 Another anti-fungal agent is griseofulvin, a fungistatic agent which is

WEST

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L2: Entry 5 of 5 File: USPT Jan 12, 1999

DOCUMENT-IDENTIFIER: US 5858974 A
TITLE: Anti-fungal peptides

US Patent No. (1):
5858974

Brief Summary Text (19):
Mucormycosis is an acute suppurative opportunistic mycosis that produces rhinocerebral, pulmonary or disseminated disease in immunocompromised patients, and local or disseminated disease in patients with burns or open wounds. Infection is caused by fungi in the class Zygomycetes, and include Basidiobolus, Conidiobolus, Rhizopus, Mucor, Absidia, Mortierella, Cunninghamella, and Saksenaea. Rhinocerebral mucormycosis accounts for about half of all cases of mucormycosis. It is one of the most rapidly fatal fungal diseases, with death occurring within 2-10 days in untreated patients. Early clinical signs include nasal stuffiness, bloody nasal discharge, facial swelling and facial pain. The infection then spreads to the eyes, cranial nerves and brain. Pulmonary mucormycosis is nearly as common as rhinocerebral disease and manifests with the same necrotizing and infarction as aspergillosis. Fungi are virtually never seen or cultured from blood, sputum or cerebrospinal fluid. Disseminated mucormycosis may follow pulmonary or burn wound infection. Treatment is with amphotericin B.

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L2: Entry 5 of 5 File: USPT Jan 12, 1999

US-PAT-NO: 5858974
DOCUMENT-IDENTIFIER: US 5858974 A

TITLE: Anti-fungal peptides

DATE-ISSUED: January 12, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Little, II; Roger G.	Benicia	CA		
Lim; Edward	Walnut Creek	CA		
Fadem; Mitchell B.	Carmel Valley	CA		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
XOMA Corporation	Berkeley	CA			02

APPL-NO: 08/ 621259 [PALM]
DATE FILED: March 21, 1996

PARENT-CASE:
This is a continuation-in-part of U.S. patent application Ser. No. 08/504,841 filed Jul. 20, 1995 now pending, herein incorporated by reference.

INT-CL: [06] A61 K 38/00, A61 K 38/02, C07 K 5/00, C07 K 7/00

US-CL-ISSUED: 514/12; 514/9, 514/11, 514/13, 514/14, 514/15, 514/16, 514/17, 530/317, 530/324, 530/327, 530/328, 530/329
US-CL-CURRENT: 514/12; 514/11, 514/13, 514/14, 514/15, 514/16, 514/17, 514/9, 530/317, 530/324, 530/327, 530/328, 530/329

FIELD-OF-SEARCH: 530/324, 530/325, 530/327, 530/326, 530/328, 530/329, 530/317, 514/12, 514/13, 514/14, 514/15, 514/16, 514/17, 514/9, 514/11

PRIOR-ART-DISCLOSED:

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Search Selected Search ALL

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☐	5171739	December 1992	Scott et al.	514/12
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ART-UNIT: 164

PRIMARY-EXAMINER: Davenport; Avis M.

ATTY-AGENT-FIRM: McAndrews, Held & Malloy, Ltd.

ABSTRACT:

The present invention relates generally to anti-fungal peptides derived from or based on Domain III (amino aids 142-169) of bactericidal/permeability-increasing protein (BPI) and in vivo or in vitro uses of such peptides.

15 Claims, 10 Drawing figures

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FILE 'USPAT' ENTERED AT 13:21:50 ON 22 SEP 1999

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*        U. S.   P A T E N T   T E X T   F I L E                       *
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E#      FILE            FREQUENCY  TERM
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E1      USPAT                1      PONICI, ADRIAN IOAN/IN
E2      USPAT                1      PONIECKI, ANDY/IN
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E4      USPAT                1      PONIKELSKY, ZDENEK/IN
E5      USPAT                6      PONIKWIA, EDWARD F/IN
E6      USPAT                1      PONINEAU, BERNARD/IN
E7      USPAT                1      PONINSKI, CARL L/IN
E8      USPAT                1      PONISCH, JURGEN/IN
E9      USPAT                1      PONISCH, MARTIN/IN
E10     USPAT                1      PONITZ, GERD/IN
E11     USPAT                2      PONITZ, WILFRIED/IN
E12     USPAT                2      PONITZSCH, WERNER/IN

=> s(intestinal mucositis or mucositis)

'S(INTESTINAL' IS NOT A RECOGNIZED COMMAND

=> s (intestinal mucositis or mucositis)

         14792 INTESTINAL
           151 MUCOSITIS
             1 INTESTINAL MUCOSITIS
                 (INTESTINAL(W)MUCOSITIS)
           151 MUCOSITIS
L1         151 (INTESTINAL MUCOSITIS OR MUCOSITIS)

=> s (intestinal mucositis or mucositis)/clm

           858 INTESTINAL/CLM
            13 MUCOSITIS/CLM
             0 INTESTINAL MUCOSITIS/CLM
                 ((INTESTINAL(W)MUCOSITIS)/CLM)
            13 MUCOSITIS/CLM
L2          13 (INTESTINAL MUCOSITIS OR MUCOSITIS)/CLM

=> s (antifungal or antifung?)

          7082 ANTIFUNGAL
          7716 ANTIFUNG?
L3        7716 (ANTIFUNGAL OR ANTIFUNG?)

=> s (antifungal or antifung?)/clm

           834 ANTIFUNGAL/CLM
           983 ANTIFUNG?/CLM
L4         983 (ANTIFUNGAL OR ANTIFUNG?)/CLM

=> s l1 and l3

L5          16 L1 AND L3

=> s l2 and l4

L6           0 L2 AND L4

=> d l5 1-16
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3. 5,801,181, Sep. 1, 1998, Amino alcohol substituted cyclic compounds; John Michnick, et al., 514/263, 183, 249, 259, 274, 309, 315, 418, 425, 617, 619, 626, 668, 669 [IMAGE AVAILABLE]

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5. 5,726,156, Mar. 10, 1998, Cytokine regulatory agents and methods of use in pathologies and conditions associated with altered cytokine levels; Beverly E. Girten, et al., 514/16, 17, 18; 530/317, 322, 329, 330 [IMAGE AVAILABLE]

6. 5,652,337, Jul. 29, 1997, OP-3-induced morphogenesis; Hermann Oppermann, et al., 530/350, 399 [IMAGE AVAILABLE]

7. 5,652,118, Jul. 29, 1997, Nucleic acid encoding a novel morphogenic protein, OP-3; Engin Ozkaynak, et al., 435/69.1, 70.1, 70.3, 71.1, 71.2, 252.3, 252.33, 320.1, 325, 348, 358, 360, 365.1, 366; 536/23.5 [IMAGE AVAILABLE]

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9. 5,478,814, Dec. 26, 1995, Hemorrhoidal, other compositions and methods of treatment; Elias W. Packman, 514/53, 882, 946, 947, 960 [IMAGE AVAILABLE]

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11. 5,466,680, Nov. 14, 1995, Method and compositions for enhancing white blood cell functioning on a mucosal or cutaneous surface; Michael A. Rudy, 514/57, 781, 866, 885, 887, 917, 921, 925, 926, 927, 928, 931, 932, 933, 934 [IMAGE AVAILABLE]

12. 5,407,663, Apr. 18, 1995, Method of treating inflammatory conditions of the mouth using steroid containing mouthwash which may contain **antifungal** agents; Drore Eisen, 424/49; 514/171 [IMAGE AVAILABLE]

13. 5,310,545, May 10, 1994, Method of treatment using mouthwashes containing steroids and **antifungal** agents and compositions of matter; Drore Eisen, 424/49; 514/171 [IMAGE AVAILABLE]

14. 5,196,405, Mar. 23, 1993, Compositions and methods of treating hemorrhoids and wounds; Elias W. Packman, 514/53, 882 [IMAGE AVAILABLE]

15. 4,961,926, Oct. 9, 1990, Methods for prevention and treatment of **mucositis** with granulocyte colony stimulating factor; Janice L. Gabrilove, 424/85.1; 514/2, 8, 21, 917, 922; 600/1 [IMAGE AVAILABLE]

16. 4,945,084, Jul. 31, 1990, Method and composition for topically treating anorectal or other dermal wounds; Elias W. Packman, 514/53, 882 [IMAGE AVAILABLE]

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16. 4,945,084, Jul. 31, 1990, Method and composition for topically treating anorectal or other dermal wounds; Elias W. Packman, 514/53, 882 [IMAGE AVAILABLE]

US PAT NO: 4,945,084 [IMAGE AVAILABLE] L5: 16 of 16

ABSTRACT:
Hemorrhoidal . . . the symptoms of hemorrhoids in humans. Compositiions containing disaccharide polysulfate-aluminum compounds such as sucralfate, alone or in combination with antibiotics, **antifungal** agents, anti-acne agents, or local anesthetics as an active agent effective in promoting the healing of wounds which are not. . .

SUMMARY:

BSUM(12)

A . . . for a wound and also acts as a carrier for materials such as antibiotics, local anesthetics, antihistamines, antiacne materials and **antifungal** materials.

SUMMARY:

BSUM(24)

In addition, oral ulcers or **mucositis** which have developed as a direct consequence of treatment of patients receiving chemotherapy or radiation or both have been treated. . .

SUMMARY:

BSUM(53)

It . . . area thereby holding the additional pharmaceutical compound near the wound. In this manner for example, an antibiotic, a steroid, an **antifungal** agent, a biocidal agent, a local anesthetic or an anti-acne agent or a combination thereof is applied topically to a. . .

CLAIMS:

CLMS(15)

15. The composition of claim 14, further including an antibiotic, an **antifungal** agent, a steroid, a biocide, a topical anesthetic, or an anti-acne agent.

CLAIMS:

CLMS(27)

27. . . . selected from the group consisting of an antibiotic, a local anesthetic, an antihistamine, an anti-acne agent a steroid and an **antifungal** agent.

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L5: Entry 29 of 30 File: USPT Apr 14, 1998

DOCUMENT-IDENTIFIER: US 5739107 A
TITLE: Morphogen treatment of gastrointestinal ulcers

Brief Summary Text (4):
The luminal lining of the mammalian gastrointestinal tract (GI tract), which extends from the mouth cavity to the rectum, includes a protective layer of continually proliferating basal epithelial cells overlying a mucosal layer. Together, the basal epithelium and mucosa create the protective "gastrointestinal barrier." Disruption of this barrier results in lesions that can become infected and/or expose underlying tissue to the corrosive effect of gastric juices. Gastrointestinal ulcerations can cause oral mucositis, gastric ulcers, necrotizing enterocolitis, regional ileitis, ulcerative colitis, regional enteritis (Crohn's disease), proctitis, and other forms of inflammatory bowel disease (IBD).

Brief Summary Text (9):
Gastointestinal ulcer disease, in particular, peptic ulcers, affect 5-15% of the United States population. Peptic ulcers include gastric ulcers, which occur as lesions in the wall of the stomach, and duodenal ulcers, which are deep lesions that occur in the wall of the duodenum, i.e., the upper portion of the small intestine. Another ulcer disease, particularly worrisome to pediatricians, occurs in the premature infants. This condition, known as necrotizing enterocolitis, affects 10-15% of newborns having a birth weight of under 1.5 kg and results in severe ulceration of the small intestine, which frequently requires surgery. Gastric ulcers can result from an imbalance in factors which maintain the natural gasatrointestinal barrier, including factors which neutralize corrosive gastric juices, such as the mucous bicarbonate, and other factors which protect the body from luminal damaging agents. Although current antiulcer therapeutics, including antisecretory products such as cimetidine and ranitidine, appear to be effective in healing duodenal ulcers, it is generally believed that they are effective because they reduce normal gastric acid secretion. While the reduction in acidity aids in the closure of the ulcer, it also interferes with normal digestion. Accordingly, a high percentage of ulcers healed with current therapies recur within one year of therapy. The high rate of ulcer recurrence is thought to be at least partially attributable to the reduced number of mucus-producing cells in the scar tissue which is left at the site of the healed ulcer, rendering the area more vulnerable to rupture when the gastointestinal acidity returns to normal.

Brief Summary Text (11):
Severe ulceration of the gastrointestinal mucosa also can spontaneously occur in the lower bowel (distal ileum and colon) in a spectrum of clinical disorders called inflammatory bowel disease (IBD). The two major diseases in this classification are ulcerative colitis and regional enteritis (Crohn's Disease) which are associated with severe mucosal ulceration (frequently penetrating the wall of the bowel and forming strictures and fistulas), severe mucosal and submucosal inflammation and edema, and fibrosis. Other forms of IBD include regional ileitis and proctitis. Clinically, patients with fulminant IBD can be severely ill with massive diarrhea, blood loss, dehydration, weight loss and fever. The prognosis of the disease is not good and frequently requires resection of the diseased tissue.

Brief Summary Text (18):
As used herein, "gastrointestinal tract" means the entire gastrointestinal tract of a mammal, from the mouth to the rectum, inclusive, including the mouth cavity,

esophagus, stomach, upper and lower intestines, and colon. As used herein, "ulcer" refers to an open lesion or break of the integrity of the epithelial lining of the gastrointestinal tract, resulting in erosion of the underlying mucosa. "Maintaining the integrity of the luminal lining" means providing an effective morphogen concentration to the cells of the gasatrointestinal tract luminal lining, the concentration being sufficient to substantially inhibit lesion formation in the basal epithelium of the gastrointestinal barrier, including stimulating the regeneration of damaged tissue and/or inhibiting additional damage thereto. "Protecting" mucosal tissue means providing a therapeutically effective morphogen concentration to the cells of the gastrointestinal tract luminal lining sufficient to inhibit the tissue damage associated with tissue ulceration, including stimulating regeneration of damaged tissue and/or inhibiting additional damage thereto. "Symptom-alleviating cofactor" refers to one or more pharmaceuticals which may be administered together with the therapeutic agents of this invention and which alleviate or mitigate one or more of the symptoms typically associated with periodontal tissue loss. Exemplary cofactors include antibiotics, antiseptics, anti-viral and anti-fungal agents, non-steroidal antiinflammatory agents, anesthetics and analgesics, and antisecretory agents.

Brief Summary Text (19):
In preferred embodiments of the invention, the mammal is a human and ulcers treatable according to the invention include those found in the ileum which cause regional ileitis, those found in the colon which cause ulcerative colitis, regional enteritis (Crohn's disease), proctitis and other forms of inflammatory bowel disease (IBD), gastric ulcers such as those found in the stomach, small intestines, duodenum and esophagus; and ulcers found in the mouth. The compositions and methods described herein are particularly useful in treating mucositis lesions caused by chemotherapy or radiation therapy.

Brief Summary Text (29):
Finally, the morphogens or morphogen-stimulating agents provided herein also may be administered in combination with other molecules ("cofactors"), known to be beneficial in ulcer treatments, particularly cofactors capable of ~~mitigating~~ or alleviating symptoms typically associated with ulcerated tissue damage and/or loss. Examples of such cofactors include, analgesics/anesthetics such as xylocaine, and benzocaine; antiseptics such as chlorohexidine; anti-bacterial, anti-viral and anti-fungal agents, including aminoglycosides, macrolides, penicillins, and cephalosporins; and antacids or antisecretory agents such as cimetidine or ramitidine.

Detailed Description Text (23):
Finally, the morphogens or morphogen-stimulating agents provided herein may be administered alone or in combination with other molecules known to be beneficial in treating gastrointestinal tract ulcers, particularly symptom-alleviating cofactors. Useful pharmaceutical cofactors include analgesics and anesthetics such as xylocaine, benzocaine and the like; antiseptics such as chlorohexidine; anti-viral and anti-fungal agents; and antibiotics, including aminoglycosides, macrolides, penicillins, and cephalosporins. Other potentially useful cofactors include antisecretory agents such as H2-receptor antagonists (e.g., cimetidine, ranitidine, famotidine, roxatidine acetate), muscarine receptor antagonists (e.g., Pirenzepine), and antacids such as aluminum hydroxide gel, magnesium hydroxide and sodium bicarbonate. Such agents may be administered either separately or as components of the therapeutic composition containing morphogens or morphogen-stimulating agents.

Other Reference Publication (32):
Gallagher (1991), "Oral Mucous Membrane Reactions to Drugs and Chemicals," Curr. Opn. in Dent., 1:777-782.